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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with ethylene dibromide. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1984b. Health and Environment Effects Profile for 1,2-Dibromoethane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985a. Drinking Water Criteria Document for Ethylene Dibromide (EDB). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984a).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Ethylene dibromide is a potent carcinogen in animals, causing tumors of the forestomach of rats and mice orally exposed (NCI, 1978; Van Duuren et al., 1985) and tumors of the nasal cavity of rats and respiratory tract of mice exposed by inhalation (NTP, 1982). U.S. EPA (1984b, 1985a) estimated a dose of 8×10^{-6} mg/day associated with a cancer risk of 10^{-5} for oral exposure to ethylene dibromide based on the incidence of tumors of the forestomach of male rats in the NCI (1978) experiment. A potency factor of 85 $(mg/kg/day)^{-1}$ was estimated from these data. A human q_1^* of 1.37 $(mg/kg/day)^{-1}$ was estimated for inhalation exposure by applying the multistage model of Howe and Crump (1982) to data regarding the incidence of nasal cavity tumors in male rats (NTP, 1982).

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LIST OF ABBREVIATIONS

CS	Composite score
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of ethylene dibromide are presented in Table 1-1.

In the atmosphere, ethylene dibromide should occur mostly in the vapor phase and will be decomposed by reaction with photochemically generated HO radical (NLM, 1986). The atmospheric half-life listed in Table 1-1 was calculated using a reaction rate constant of 0.25×10^{-12} cm^3/molecule-sec at 27°C and an ambient HO radical concentration of 8.0×10^5 molecules/cm^3 (Singh et al., 1981; U.S. EPA, 1986a). In water, the primary removal process for ethylene dibromide is evaporation (NLM, 1986). The aquatic half-lives listed have been calculated using a reaeration coefficient ratio of 0.53 and typical oxygen reaeration values of 0.04, 0.01 and 0.008 $hour^{-1}$ for rivers, ponds and lakes, respectively (NLM, 1986; Lyman et al., 1982). Ethylene dibromide should not significantly bioaccumulate or adsorb to sediments (NLM, 1986). In soil, it is expected to be partially removed by volatilization. Low adsorption to soil and monitoring data indicate that this compound is highly mobile in soil and may leach into groundwater, where it would tend to persist (NLM, 1986).

TABLE 1-1

Selected Chemical and Physical Properties
and Environmental Fate of Ethylene Dibromide

Property	Value	Reference
CAS number:	106-93-4	
Chemical class:	halogenated aliphatic compound	
Molecular weight:	187.88	
Vapor pressure:	11.7 mm Hg (25°C)	Jaber et al., 1984
Water solubility:	4300 mg/ℓ (25°C)	Jaber et al., 1984
Log octanol/water partition coefficient:	1.76 (estimated)	Jaber et al., 1984
Bioconcentration factor:	<1 (carp, Cyprinus carpio)	Kawasaki, 1980
Soil adsorption coefficient:	14-160	NLM, 1986
Half-lives in		
Air:	40 days (estimated)	Singh et al., 1981; U.S. EPA, 1986a
Water:	32 hours (river) (estimated) 130 hours (lake) (estimated) 163 hours (pond) (estimated)	NLM, 1986; Lyman et al., 1982
Soil:	NA	

NA = Not available

2. ABSORPTION FACTORS IN HUMAN AND EXPERIMENTAL ANIMALS

2.1. ORAL

Plotnick et al. (1979) administered a single gavage dose of 15 mg/kg ^{14}C-ethylene dibromide in corn oil to young adult male Sprague-Dawley rats and measured the excretion of radioactivity in the urine and feces during the following 48 hours. Fecal excretion accounted for only 1.65% of the administered dose of radioactivity, suggesting that ethylene dibromide was almost completely absorbed from the gastrointestinal tract.

2.2. INHALATION

Pertinent data regarding the rate or extent of absorption of ethylene dibromide could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. NCI (1978) administered ethylene dibromide in corn oil by gavage to groups of 5 male and 5 female Osborne-Mendel rats and equal numbers of B6C3F1 mice at 0, 40, 63, 100, 163 or 251 mg/kg, 5 days/week for 6 weeks followed by a 2-week observation period. In rats, mortality occurred at ≥100 mg/kg. Mean final body weights were within 10% of those of controls at ≤63 mg/kg. The observations in mice are more difficult to interpret because of an apparent discrepancy in the data. Although the dosages administered appear to be those stated above, NCI (1978) reported that no mortality occurred in males at ≤159 mg/kg. Deaths occurred in one 251 mg/kg female and one 100 mg/kg female. Effects on body weights were inconsistent. At ≤159 mg/kg, terminal body weights of females were greater than those of controls. Males at 63 and 159 mg/kg had terminal body weights 71 and 91% that of controls, respectively.

In another subchronic study using B6C3F1 mice, Van Duuren et al. (1985) administered ethylene dibromide in drinking water at 2.7, 5.3 or 10.6 mM (507, 996 or 1992 mg/L) to groups of 5 males and 5 females for 3 months. Water consumption was measured for mice at the two higher dose levels and was determined to be 2.6 and 4.0 mL/mouse/day for males and females, respectively, at 5.3 mM, and 4.0 and 3.8 mL/mouse/day for males and females, respectively, at 10.6 mM. All mice survived. Terminal body weights were 24-26 g for females and 28-29 g for males. The authors reported that body weights of males were slightly depressed and that the histopathological appearance of the forestomach at the end of 1 and 3 months was "unusual"; further information was not available. Since starting or average body weights were not provided, estimation of dose on an mg/kg/day basis is not possible.

Aman et al. (1946) treated an unspecified number of rats and guinea pigs by gavage with 40-50 mg/kg/day of ethylene dibromide in oil or in 50% aqueous alcohol for ~4 months and reported no adverse effects including body weight changes. The results of the study are inconclusive, however, because the study was incompletely reported (numbers of animals/groups not specified) and no evaluation of gross or histological examination was performed.

3.1.2. Inhalation. Three subchronic studies (Reznick et al., 1980; Nitschke et al., 1981; Rowe et al., 1952) evaluated the toxicity of inhaled ethylene dibromide to rats, mice, guinea pigs, rabbits and monkeys. In the range-finding study for the chronic carcinogenicity bioassay of ethylene dibromide (NTP, 1982), Reznick et al. (1980) and NCI (1978) exposed groups of 4-6 F344 rats and 10 B6C3F1 mice/sex to 0, 3, 15 or 75 ppm (0, 23, 115 or 580 mg/m³) of ethylene dibromide for 6 hours/day, 5 days/week for 13 weeks. There was a concentration-related depressed weight gain in male rats, but weight gain was depressed in female rats only at the highest level. No effect on mortality was observed in the rats; an increased mortality rate was observed in low-dose male and high-dose female mice. Nasal cavity alterations such as cytomegaly; focal hyperplasia, squamous metaplasia and loss of cilia were observed in the high-dose groups of both species, but were absent in the control, medium- and low-dose groups. In addition, swelling and vacuolization of adrenal cortical cells was observed in the high-dose rats.

The U.S. EPA (1980b) reported the study by Nitschke et al. (1981) in which an unspecified number of male and female rats were exposed to 0, 23, 77 or 3076 mg/m³ for 6 hours/day, 5 days/week for 13 weeks. Decreased body weight gain, increased liver and kidney weights, and epithelial hyperplasia and squamous metaplasia of the nasal cavity were observed at 3076

mg/m³. Slight, reversible epithelial hyperplasia was observed in the nasal cavity of rats exposed to 77 mg/m³. No adverse effects were observed in rats exposed to 23 mg/m³.

Rowe et al. (1952) exposed rats (20/sex/group), guinea pigs (8/sex/group), rabbits (3 males, 1 female/group) and monkeys (1/sex/group) to 0, 25 or 50 ppm (0, 190 or 380 mg/m³) of ethylene dibromide for 7 hours/day, 5 days/week for experimental periods varying from 213-220 days at 25 ppm and 70-91 days at 50 ppm. The toxicological parameters investigated were general appearance and behavior, growth rate, organ and body weights, and histology of various organs including liver, kidney, lung, adrenals and testes, but not the nasal cavity. No treatment-related adverse effects were observed in any species at 25 ppm. High mortality from infections of the respiratory tract was observed in both sexes of exposed guinea pigs and in male rats. At 50 ppm, increased liver and kidney weights (both sexes), increased lung weights (males), decreased testicular weight and decreased spleen weight (females) were observed in the rats. High mortality, attributed to infections of the respiratory tract, occurred in 10/20 male and 4/20 female rats. Decreased body weight gain, slight central fatty degeneration of the liver and renal tubular epithelium degeneration were observed in the guinea pigs. Rabbits and monkeys had slight increases in liver weights. The investigators concluded that rabbits and monkeys and "probably" rats and guinea pigs tolerated the 25 ppm exposure without adverse effects.

3.2. CHRONIC

3.2.1. Oral. In a cancer bioassay (NCI, 1978), groups of 50 male and 50 female Osborne-Mendel rats and identical numbers of B6C3F1 mice were treated by gavage with ethylene dibromide in corn oil. The TWA dosages received by male rats were 27.4 or 29.1 mg/kg/day; by female rats, 26.7 or 28.1 mg/kg/day; and by male and female mice, 0, 43.9 or 76.6 mg/kg/day. Controls

consisted of 20 animals/sex/species. (Further details are provided in Section 4.2.1.) Dose-related weight depression and early mortality was observed in the rats and mice, but may have been tumor-related. Treatment-related, but not dose-related, changes (peliosis hepatis) occurred in the livers of male but not female rats. Adrenal cortical degeneration was observed in a small number of treated male and female rats. No adrenal effects were observed in mice. Although the incidence of testicular degeneration was not increased in treated rats, testicular degeneration occurred at an earlier age in the ethylene dibromide treated rats compared with controls. Testicular atrophy occurred in the mice only at the high dose level.

3.2.2. Inhalation. Two studies (NTP, 1982; Wong et al., 1982) designed primarily to evaluate the carcinogenicity of ethylene dibromide also reported nonneoplastic effects of inhalation exposure to ethylene dibromide. In the NTP (1982) bioassay, groups of 50 F344 rats and 50 B6C3F1 mice were exposed to 0, 10 or 40 ppm (0, 77 or 310 mg/m^3) ethylene dibromide (99.3-99.4% pure) 5 hours/day, 5 days/week for 78-106 weeks. Weight depression was observed in mice and rats of both sexes. Increased mortality rate was observed in male and female rats exposed to the high dose level, in male mice exposed to the low dose level, and in female mice exposed to both dose levels. The incidence of liver necrosis and renal toxic degeneration was significantly increased in male and female rats and in female mice exposed to the high dose level. The incidence of testicular degeneration was significantly increased in the rats exposed to both dose levels, but was not altered in mice exposed to ethylene dibromide. Female rats had an increased incidence of adrenal cortical degeneration at the high dose level and an increased incidence of retinal atrophy at both dose levels tested. Rats and mice of both sexes had inflammatory and hyperplastic lesions in the respiratory epithelium.

In the Wong et al. (1982) study, groups of 48 Sprague-Dawley rats/sex were exposed to 0 or 20 ppm (0 or 154 mg/m³) of ethylene dibromide (99% purity) for 7 hours/day, 5 days/week for 18 months. Body weight and survival rate were decreased in treated males and females. Testicular atrophy was not observed in treated rats. Hematological parameters appeared normal in both males and females after 10-12 months of exposure. The nasal cavity was not evaluated in the Wong et al. (1982) study.

3.3. TERATOGENIC AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenic effects of ethylene dibromide after ingestion could not be located in the available literature. The antispermatogenic effect of ingesting ethylene dibromide, as evidenced by structurally abnormal sperm displaying low motility and density and a depopulation of the seminiferous tubules, was observed in bulls (Amir and Volcani, 1965, 1967); these effects were reversible (Amir and Ben-David, 1973; Amir, 1975; Amir et al., 1977, 1979). Ingestion of ethylene dibromide by rams has not resulted in adverse spermatogenic effects (Amir and Ben-David, 1973). NCI (1978) reported an earlier onset of testicular atrophy in rats and an increased incidence of testicular atrophy at the high dose level in mice treated chronically by gavage.

3.3.2. Inhalation. Two inhalation studies (Short et al., 1976, 1978) reviewed in detail by the U.S. EPA (1984b, 1985a), indicate that ethylene dibromide is teratogenic in rats and mice. A third study evaluated the behavioral effects of ethylene dibromide on pups of exposed rats (Smith and Goldman, 1983). In the first study, groups of 17-18 pregnant Charles River CD rats and 9-17 pregnant CD-1 mice were exposed to 0 (diet ad libitum), 0 (diet restricted) or 32 ppm (246 mg/m³) of ethylene dibromide for 23 hours/day on days 6-15 of gestation (Short et al., 1976). The rats and mice

were sacrificed on gestational days 20 and 18, respectively. Significantly decreased food consumption and body weight gain, but no effect on the mortality rate, was observed in the dams of both species. No effect on fetal weight was observed in rats or mice. Litter size was significantly decreased in rats, but not mice, exposed to ethylene dibromide. In addition, a significantly increased incidence of hydrocephaly, wavy ribs and extra ribs was observed in the pups of rats exposed to ethylene dibromide during gestation. Similar effects were not observed in pups from rats fed the restricted diets. Although the incidence of skeletal anomalies and hydrocephaly was significantly increased in the fetuses of mice compared with unrestricted diet fed controls, the biological significance of this result is difficult to interpret because of the increased incidence of skeletal anomalies and hydrocephaly in the diet-restricted mice.

In the second study (Short et al., 1978), groups of 11-17 pregnant Charles River CD rats and 9-19 pregnant CD-1 mice were exposed to 0 (diet ad libitum), 0 (diet restricted), 20, 38 or 80 ppm (154, 292 or 615 mg/m³) of ethylene dibromide for 23 hours/day on days 6-15 of gestation. The rats and mice were sacrificed on gestational days 20 and 18, respectively. The maternal mortality rate was 50 and 100% for the rats and mice, respectively, exposed to 80 ppm, and 41% for the mice exposed to 38 ppm of ethylene dibromide. No live pups or viable fetuses were obtained from the rats exposed to 80 ppm. Decreased numbers of viable fetuses/litter were observed in the rats exposed to 80 ppm and in the mice exposed to 80 and 38 ppm. An increased incidence of resorptions was observed in rats exposed to 80 ppm and in mice exposed to all levels of ethylene dibromide tested. Decreased fetal body weight was observed in the rats exposed to 38 ppm and in the mice exposed to 20 and 38 ppm.

Groups of 16 pregnant Long-Evans rats were exposed to 0, 0.43, 6.67 or 66.67 ppm (3.3, 51.3 or 512.3 mg/m³) of ethylene dibromide 4 hours/day, 3 days/week from day 3-20 of gestation (Smith and Goldman, 1983). Behavioral testing of the pups (rotorod, open field activity, straight alley activity, T-maze discrimination and passive avoidance) was performed at intervals between 30 and 100 days postpartum. Decreased gestational weight gain of dams, enhanced rotorod and T-maze discrimination were observed in the middle- and high-dose groups. No behavioral effects were observed at the lowest dose level evaluated. No effect on litter size was observed at any dose level evaluated.

To evaluate the effect of inhaled ethylene dibromide on reproduction, groups of 18-20 male Charles River CD rats were exposed to 19, 38 or 89 ppm (146, 292 or 684 mg/m³) of ethylene dibromide for 7 hours/day, 5 days/week for 10 weeks (Short et al., 1979). Half of the males were killed after exposure and their serum testosterone levels and testicular histology were examined. The remaining exposed males were mated to females who had been exposed to 0, 20, 39 or 80 ppm (0, 154, 300 or 615 mg/m³) for 7 hours/day, 7 days/week for 3 weeks. Males exposed to 89 ppm (684.0 mg/m³) of ethylene dibromide had reduced food consumption, reduced serum testosterone concentrations and atrophy of the reproductive organs, and failed to impregnate any females; the females exposed to 80 ppm (615 mg/m³) had abnormal estrus cycles during exposure. No adverse reproductive effects were observed at lower exposure levels in either males or females.

In the carcinogen bioassay in which rats and mice were exposed to 0.10 or 40 ppm (NTP, 1982) (Chapter 4), the incidence of testicular atrophy was significantly increased in the F344 rats at both dose levels, but not in the B6C3F1 mice. Wong et al. (1982) reported that an increased incidence of

testicular atrophy was not observed in the Sprague-Dawley rats exposed to 20 ppm (154 mg/m³) of ethylene dibromide for 7 hours/day, 5 days/week for 18 months. Both studies used exposure levels of ethylene dibromide sufficiently high to be associated with a significantly increased incidence of cancer in F344 and Sprague-Dawley and B6C3F1 mice.

3.4. TOXICANT INTERACTIONS

Administration of either of two cytochrome P-450 inhibitors, disulfiram and diethyldithiocarbamate, enhances the carcinogenicity and hepatic and testicular toxicity of ethylene dibromide (Wong et al., 1982; Nachtomi, 1980, 1981). Conversely, pretreatment of rats with the microsomal enzyme inducer, phenobarbital, decreased the hepatic toxicity of ethylene dibromide (Nachtomi, 1980, 1981).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenic potential of ethylene dibromide to orally exposed humans could not be located in the available literature.

4.1.2. Inhalation. No statistically significant effect on the mortality rate or the incidence of cancer or respiratory disease was associated with occupational exposure to ethylene dibromide in one published study (Ott et al., 1980) and two unpublished studies (Ter Haar, 1978). Further details of the studies are reported in U.S. EPA (1985a). The interpretation of the results of these studies, however, is complicated by small population size, poorly quantified levels of exposure and concomitant exposure to numerous other chemicals.

4.2. BIOASSAYS

4.2.1. Oral. Significantly increased incidences of a variety of tumors in rats and mice were reported in the NCI (1978) oral bioassay of ethylene dibromide. Technical grade ethylene dibromide (purity 96.3-99.6%) was administered in corn oil by gavage to groups of 50 Osborne-Mendel rats/sex and 50 B6C3F1 mice/sex. Initially, rats of both sexes were treated with 40 or 80 mg/kg, 5 days/week, and mice of both sexes were treated with 60 or 120 mg/kg, 5 days/week. Groups of 20 rats/sex and 20 mice/sex served as untreated controls. Identical groups were maintained as vehicle treated controls. Early mortality in the high-dose rats prompted a 13-week suspension of treatment after 16 weeks, and a subsequent re umption of treatment at the same dosage t..at the low-dose rats were receiving, resulting in TWA doses of 38 and 41 mg/kg, 5 days/week for low- and high-dose males, and 37 and 39 mg/kg, 5 days/week for low- and high-dose females, respectively.

Male rats were terminated after 49 weeks and female rats were terminated after 61 weeks of treatment. No observation period following the treatment period was provided. Alterations in the dosage level administered to mice resulted in TWA doses of 62 and 107 mg/kg, 5 days/week in low- and high-dose groups, respectively. Treatment of mice continued for 53 weeks; observation periods without treatment were 24 weeks for high-dose males, 25 weeks for low-dose males and high-dose females, and 37 weeks for low-dose females. As summarized in Table 4-1, significantly increased incidences of squamous cell carcinomas of the forestomach (both species, both sexes), hepatocellular carcinomas and neoplastic nodules of the liver (female rats), hemangiosarcomas of the circulatory system (male rats) and alveolar/bronchiolar adenomas (mice, both sexes) were observed. Squamous cell carcinomas of the forestomach in the rats appeared as early as 12-15 weeks after the start of treatment, and occurred in 97-100% of the high-dose males and the low- and high-dose females that survived beyond 15 weeks of treatment. Forestomach carcinomas developed in 78-92% of the male mice that survived 26 weeks and in 76-100% of the female mice that survived 14-18 weeks of treatment.

Van Duuren et al. (1985) noted an increased incidence of stomach tumors in B6C3F1 mice exposed to ethylene dibromide in drinking water for 15-17 months. In this experiment, 30 males and 30 females were provided drinking water containing ethylene dibromide (>99% pure) that supplied 116 and 103 mg/kg/day, respectively, until spontaneous death or sacrifice at 15 months (males) or 17 months (females). Distilled water-treated controls consisted of 50 mice/sex, apparently sacrificed at 18 months. The concentration of ethylene dibromide in the drinking water depressed water consumption by 25% in the males and 34% in the females. The investigators determined that males consumed ethylene dibromide at 116 and females at 103 mg/kg/day.

TABLE 4-1

Summary of Oral Carcinogenicity Bioassay of Ethylene Dibromide[a]

Species/Strain	Sex	Dose or Exposure[b] (mg/kg/day)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound[c]	Target Organ	Tumor Type	Tumor Incidence[d] (p value)
Rats/ Osborne-Mendel	M	29	49	49	96.3-99.6%	forestomach circulatory system	carcinoma[e] hemangiosarcoma	33/50 (p<0.001) 4/27[f] (NS)
	M	27	49	49	96.3-99.6%	forestomach circulatory system	carcinoma[e] hemangiosarcoma	45/50 (p<0.001) 11/50[f] (p=0.018)
	M	0 (vehicle control)	49	63	NA	forestomach circulatory system	carcinoma[e] hemangiosarcoma	0/20 (p<0.001) 0/20[f] (NS)
	F	28	61	61	96.3-99.6%	forestomach liver	carcinoma[e] carcinoma[g] carcinoma/nodules[g,h]	29/50 (p<0.001) 5/25[f] (p=0.043) 6/25[f] (p=0.022)
	F	26	61	61	96.3-99.6%	forestomach liver	carcinoma carcinoma carcinoma/nodules	40/50 (p<0.001) 1/35[f] (NS) 1/35[f] (NS)
	F	0 (vehicle control)	61	63	NA	forestomach liver	carcinoma carcinoma carcinoma/nodules	0/20 (p<0.01) 0/20[f] (p=0.028) 0/20[f] (p=0.014)
Mice/B6C3F1	M	76	53	77	96.3-99.6%	forestomach forestomach lung	carcinoma[e] papilloma or carcinoma[e] adenoma[i]	29/49 (p<0.001) 3/149 (p<0.001) 10/47 (p=0.021)
	M	44	53	77	96.3-99.6%	forestomach forestomach lung	carcinoma papilloma or carcinoma adenoma	45/50 (p<0.001) 45/50 (p<0.001) 4/45 (NS)
	M	0 (vehicle control)	53	59	NA	forestomach forestomach lung	carcinoma papilloma or carcinoma adenoma	0/20 (p=0.003) 0/20 (p=0.001) 0/20 (p=0.009)
	F	76	53	80	96.3-99.6%	forestomach lung	carcinoma[e] adenoma[i]	28/50 (p<0.001) 4/14[f] (p=0.024)

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TABLE 4-1 (cont.)

Species/Strain	Sex	Dose or Exposure[b] (mg/kg/day)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound[c]	Target Organ	Tumor Type	Tumor Incidence[d] (p value)
Mice/B6C3F1	F	44	53	78	96.3-99.6%	forestomach lung	carcinoma adenoma	46/49 (p<0.001) 2/10[f] (NS)
	F	0 (vehicle control)	53	60	NA	forestomach	carcinoma adenoma	0/20 (p=0.011) 0/19[f] (p=0.018)

[a]Source: NCI, 1978

[b]Reported TWA doses were multiplied by 5/7 to give a more accurate daily dose (the reported TWA doses reflected gavage treatment on 5 consecutive days/week).

[c]Vehicle was corn oil (intubation) in all cases

[d]Incidences of most frequently appearing tumors were tabulated. The probability levels for the Fischer exact and Cochran-Armitage tests are given beneath the incidence of tumors in the treated groups and control group, respectively, when p<0.05; otherwise, NS (not significant) is indicated.

[e]Squamous-cell carcinomas

[f]Time-adjusted incidence because of early mortality

[g]Hepatocellular carcinomas

[h]Preneoplastic nodules

[i]Alveolar/bronchiolar adenomas

NA = Not applicable; NS = not significant

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Survival was depressed in treated mice, which was attributed to the development of stomach tumors. Necropsy and histopathological examination revealed these tumors to be papillomas and squamous cell carcinomas of the forestomach. Detailed results are presented in Table 4-2. Other statistically significant increased incidences of tumors included tumors in the glandular stomach and liver of males and the liver of females, but these all represented extension or metastases of squamous cell carcinomas from the forestomach.

4.2.2. Inhalation. The chronic inhalation bioassays (NTP, 1982; Wong et al., 1982; Stinson et al., 1981) indicate that ethylene dibromide is associated with an increased incidence of tumors in rats and mice. Groups of 50 F344 rats/sex and 50 B6C3F1 mice/sex were exposed to 0, 10 or 40 ppm (0, 77 or 307 mg/m^3) of ethylene dibromide (99.3-99.4% pure) 6 hours/day, 5 days/week for 78-106 weeks (NTP, 1982). Details are summarized in Table 4-3. Chronic inhalation of ethylene dibromide was associated with a significantly increased incidence of nasal tumors in both male and female rats at both dose levels, as well as hemangiosarcomas (splenic) and mesotheliomas (tunica vaginalis) in male rats exposed to the high dose level, mammary fibroadenomas in females exposed to both dose levels, and bronchiolar/alveolar carcinomas or adenomas and hemangiosarcomas in female rats exposed to the high dose level. Chronic inhalation of ethylene dibromide was associated with a significantly increased incidence of adenomas or carcinomas in the respiratory system of male mice exposed to the highest dose level and of female mice exposed to both dose levels; subcutaneous fibrosarcomas, hemangiosarcomas and mammary adenocarcinomas in female mice exposed to both dose levels; and nasal carcinomas in female mice exposed to the high dose level only. For specific incidences and tumor types, see Table 4-3.

TABLE 4-2

Incidence of Tumors of the Forestomach in Male and Female B6C3F1 Mice Exposed to Ethylene Dibromide (>99% purity) in the Drinking Water[a]

Sex	Dose[b] (mg/kg/day)	Duration of Treatment (days)	Duration of Experiment (days)	Tumor Type	Tumor Incidence (p value)[c]
M	0 (control)	NA	550	papilloma	1/45 (NA)
				squamous cell carcinoma	0/45 (NA)
				combined papilloma and squamous cell carcinoma	1/45 (NA)
M	116	456	456	papilloma	0/28 (NA)
				squamous cell carcinoma	26/28 (p<0.0005)
				combined papilloma and squamous cell carcinoma	26/28 (p<0.0005)
F	0 (control)	NA	561	papilloma	1/50 (NA)
				squamous cell carcinoma	0/50 (NA)
				combined papilloma and squamous cell carcinoma	1/50 (NA)
F	103	512	512	papilloma	5/29 (NR)
				squamous cell carcinoma	22/29 (NR)
				combined papilloma and squamous cell carcinoma	27/29 (p<0.0005)

[a]Source: Van Duuren et al., 1985

[b]Data provided by investigators

[c]Calculated by chi-square analysis

NA = Not applicable; NR = not reported

TABLE 4-3

Summary of Oral Carcinogenicity Bioassay of Ethylene Dibromide[a]

Species/ Strain	Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Rats/F344	M	40	88	88-89	99.3-99.4%	vapor	nasal cavity	carcinoma	21/50 (p<0.001)
								adenocarcinoma	20/50 (p<0.001)
								tumors[d]	41/50 (p<0.001)
							circulatory system	hemangiosarcoma	15/50 (p<0.001)
							tunica vaginalis	mesothelioma or malignant	25/50 (p<0.001)
	M	10	103	104	99.3-99.4%	vapor	nasal cavity	carcinoma	0/50 (NS)
								adenocarcinoma	20/50 (p<0.001)
								tumors	39/50 (p<0.001)
							circulatory system	hemangiosarcoma	1/50 (NS)
							tunica vaginalis	mesothelioma or malignant	8/50 (p=0.15)
	M	0[e] (chamber control)	NA	104-106	NA	ambient air	nasal cavity	carcinoma	0/50 (p<0.001)
								adenocarcinoma	0/50 (p<0.001)
								tumors	0/50 (p<0.001)
							circulatory system	hemangiosarcoma	0/50 (p<0.001)
							tunica vaginalis	mesothelioma or malignant	1/50 (p<0.001)
	F	40	91	91-92	99.3-99.4%	vapor	nasal cavity	carcinoma	25/50 (p<0.001)
								adenocarcinoma	29/50 (p<0.001)
								tumors[d]	43/50 (p<0.001)
							lung	carcinoma/adenoma[f]	5/47 (p=0.024)
							circulatory system	hemangiosarcoma	5/50 (p=0.028)
							mammary gland	fibroadenoma	24/50 (p<0.001)
	F	10	103	104	99.3-99.4%	vapor	nasal cavity	carcinoma	0/50 (NS)
								adenocarcinoma	20/50 (p<0.001)
								tumors	34/50 (p<0.001)
							lung	carcinoma/adenoma	0/48 (NS)
							circulatory system	hemangiosarcoma	0/50 (NS)
							mammary gland	fibroadenoma	29/50 (p<0.001)
	F	0[e] (chamber control)	NA	104-106	NA	ambient air	nasal cavity	carcinoma	0/50 (p<0.001)
								adenocarcinoma	0/50 (p<0.001)
								tumors	1/50 (p<0.001)
							lung	carcinoma/adenoma	0/50 (p=0.001)
							circulatory system	hemangiosarcoma	0/50 (p=0.002)
							mammary gland	fibroadenoma	4/50 (p=0.002)

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TABLE 4-3 (cont.)

Species/ Strain	Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mice/B6C3F1	M	40	78	78-79	99.3-99.4%	vapor	lung	carcinoma[f]	19/46 (p<0.001)
								carcinoma/adenoma[f]	23/46 (p<0.001)
							respiratory system	tumors[g]	25/46 (p<0.001)
	M	10	78	78-79	99.3-99.4%	vapor	lung	carcinoma	3/48 (NS)
								carcinoma/adenoma	3/48 (NS)
							respiratory system	tumors	3/48 (NS)
	M	0[e] (chamber control)	NA	79	NA	ambient air	lung	carcinoma	0/41 (p<0.001)
								carcinoma/adenoma	0/41 (p<0.001)
							respiratory system	tumors	0/41 (p<0.001)
	F	40	90	90-91	99.3-99.4%	vapor	nasal cavity	carcinoma	6/50 (p=0.013)
								tumors[h]	12/50 (p<0.001)
							lung	carcinoma[f]	37/50 (p<0.001)
								carcinoma/adenoma[f]	41/50 (p<0.001)
							respiratory system	tumors[g]	42/50 (p<0.001)
							subcutaneous tissue or rib	fibrosarcoma	11/50 (p<0.001)
							circulatory system	hemangiosarcoma	23/50 (p<0.001)
								hemangiosarcoma/hemangioma	27/50 (p<0.001)
							mammary gland	adenocarcinoma	8/50 (p=0.046)
	F	10	103	104	99.3-99.4%	vapor	nasal cavity	carcinoma	0/50 (NS)
								tumors	0/50 (NS)
							lung	carcinoma	5/49 (NS)
								carcinoma/adenoma	11/49 (p=0.045)
							respiratory system	tumors	11/49 (p=0.045)
							subcutaneous tissue or rib	fibrosarcoma	5/50 (p<0.028)
							circulatory system	hemangiosarcoma	11/50 (p<0.001)
								hemangiosarcoma/hemangioma	12/50 (p<0.001)
							mammary gland	adenocarcinoma	14/50 (p=0.001)

TABLE 4-3 (cont.)

Species/ Strain	Sex	Dose or Exposure[b] (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound[c]	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (p value)
Mice/B6C3F1	F	0[e] (chamber control)	NA	104-106	NA	ambient air	nasal cavity	carcinoma	0/50 (p=0.001)
								tumors	0/50 (p<0.001)
							lung	carcinoma	1/49 (p<0.001)
								carcinoma/adenoma	4/49 (p<0.001)
							respiratory system	tumors	4/49 (p<0.001)
							subcutaneous tissue or rib	fibrosarcoma	0/50 (p<0.001)
							circulatory system	hemangiosarcoma	0/50 (p<0.001)
								hemangiosarcoma/hemangioma	0/50 (p<0.001)
							mammary gland	adenocarcinoma	2/50 (NS)

[a]Source: NTP, 1982

[b]Incidences of most frequently appearing tumors were tabulated. The probability levels for the Fischer exact and Cochran-Armitage tests are given beneath the incidence of tumors in the treated and control groups, respectively, when $p<0.05$; otherwise, NS (not significant) is indicated.

[c]Exposures were 6 hours/day, 5 days/week

[d]Includes adenomas, adenocarcinomas, adematous polyps, squamous cell carcinomas, papillary adenomas, squamous cell papillomas and carcinomas of the nose and nasal cavity.

[e]Control groups also served as controls in the bioassay of 1,2-dibromo-3-chloropropane.

[f]Alveolar/bronchiolar tumors

[g]Includes adenomas, carcinomas and adenomatous polyps of the bronchus, bronchiole and lung, and alveolar/bronchiolar adenomas and carcinomas.

[h]Includes adenomas, carcinomas, adenomatous polyps and hemangiosarcomas.

NA = Not applicable; NS = not significant

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Although the studies of Wong et al. (1982) and Stinson et al. (1981) are limited in their design, they support the association between the inhalation of ethylene dibromide and the increased incidences of tumors in rats and mice. In the Wong et al. (1982) study designed to evaluate the combined effect of ethylene dibromide inhalation and disulfiram ingestion, groups of 48 Sprague-Dawley rats of each sex were exposed to 0 or 20 ppm (0 or 154 mg/m³) ethylene dibromide (99% purity) for 7 hours/day, 5 days/week for 18 months. A significant increase in the incidence of hemangiosarcomas (splenic) and adrenal tumors (carcinoma, phenochromocytoma and cortical adenoma) were observed in both male and female rats, as well as subcutaneous tumors in males and mammary tumors (adenoma, fibroadenoma, carcinoma or adenocarcinoma) in females. The nasal cavities of the rats exposed to ethylene dibromide were not evaluated by Wong et al. (1982). In the Stinson et al. (1981) study designed to evaluate the incidence of tumors in the nasal cavity only, groups of 49-50 B6C3F1 mice/sex were exposed to 0, 10 or 40 ppm (0, 77 or 307 mg/m³) ethylene dibromide for 6 hours/day, 5 days/week for 90-103 weeks. The mice were killed within 1 week of the end of treatment. An increased incidence of nasal tumors occurred in the female mice and an increased incidence of nasal epithelial hyperplasia occurred in the male mice at the high dose level only. Neither sex had an elevated tumor incidence at the low dose level. The statistical significance of this observation is not clear, however, since no probability values were reported.

4.3. OTHER RELEVANT DATA

The mutagenic activity of ethylene dibromide has been reviewed by Fahrig (1974), IARC (1977), Rannug (1980) and the U.S. EPA (1984b, 1985a). Positive results have been reported in reverse mutation assays with Salmonella typhimurium strains G46, TA1530, TA1535 and TA100 both with and without

metabolic activation (Buselmaier et al., 1976; Brem et al., 1974; Ames and Yanofsky, 1971; Rannug et al., 1978; Stolzenberg and Hine, 1980; Van Bladeren et al., 1980; Principe et al., 1981; Shiau et al., 1980). Reduced mutagenic activity (Barber et al., 1981) or no mutagenic activity (Brem et al., 1974; Principe et al., 1981) in S. typhimurium strains TA1538 and TA98 also have been observed. Ethylene dibromide was mutagenic to Escherichia coli with or without metabolic activation (Brem et al., 1974; Hemminki et al., 1981), but reverse mutations in Bacillus subtilis occurred only in the presence of rat liver microsomal enzymes (Shiau et al., 1980). The incidence of recessive lethal mutations in Drosophila melanogaster was increased after exposure to ethylene dibromide vapor (Vogel and Chandler, 1974; Kale and Baum, 1979, 1982). Ethylene dibromide was mutagenic to cultivated mammalian cells in the absence of microsomal activation (Tezuka et al., 1980; Clive, 1973; Williams et al., 1982; Tan and Hsie, 1981; Crespi et al., 1985), but was not associated with an increased incidence of dominant lethal mutations in either rats or mice (Shirasu et al., 1984).

4.4. WEIGHT OF EVIDENCE

Based on the results of the NCI (1978) bioassay in which a significantly increased incidence in squamous cell carcinoma of the forestomach was observed in male and female Osborne-Mendel rats and B6C3F1 mice treated by gavage 5 days/week for ~1 year with ethylene dibromide, and a significantly increased incidence in nasal epithelial tumors was observed in male and female F344 rats and female B6C3F1 mice inhaling ethylene dibromide for ~2 years, ethylene dibromide is most appropriately classified in CAG Group B2 and IARC Group 2B (U.S. EPA, 1985b). CAG Group B2 chemicals are probable human carcinogens and include chemicals for which the evidence for carcinogenicity is adequate in animals but inadequate in humans (U.S. EPA, 1986).

IARC Group 2B includes chemicals for which there is sufficient evidence of carcinogenicity in animals but inadequate carcinogenicity data in humans (IARC, 1982).

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1985, 1986) has classified ethylene dibromide as an A2 chemical, indicating its potential to cause tumors in humans based on its carcinogenicity in rats and mice after oral (NCI, 1978) and inhalation (NTP, 1982) exposure. No TLV has been assigned to ethylene dibromide, but the skin notation used with ethylene dibromide indicates the potential contribution dermal absorption may have on the body burden of individuals exposed to ethylene dibromide. OSHA (1985) no longer promulgates a standard for ethylene dibromide exposure.

The U.S. EPA has suspended the use of pesticide products containing ethylene dibromide as a soil fumigant (U.S. EPA, 1983). U.S. EPA (1984b, 1985a) reports tolerances for ethylene dibromide in food products of 900 ppb for raw grain for human consumption, 150 ppb for flour and 30 ppb for ready-to-eat products.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

The results of the NCI (1978) and NTP (1982) bioassays in which ethylene dibromide was associated with significantly increased incidences of tumors in rats and mice preclude the derivation of RfD_S values for ethylene dibromide.

6.2. REFERENCE DOSE (RfD)

The results of the NCI (1978) and NTP (1982) bioassays in which rats and mice had significantly increased incidences of tumors preclude derivation of RfD values.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Carcinogenicity bioassays in laboratory animals can provide a basis for estimating the carcinogenic risk of ethylene dibromide to humans. Several studies have demonstrated the carcinogenicity of ethylene dibromide in rodents exposed by inhalation (NTP, 1982; Wong, 1982; Stinson et al., 1981), oral intubation (NCI, 1978) and dermal application. Because unequivocal evidence of carcinogenicity in man from ethylene dibromide exposure is not available, animal studies must be relied upon for assessment of the risks for humans.

The U.S. EPA (1984b, 1985a) used the data from the NCI (1978) study in the derivation of doses of ethylene dibromide associated with excess cancer risk. A high incidence of forestomach carcinoma was observed in all exposure-species-sex groups in a relatively short period of time.

To use these data, a mathematical model that incorporated variable partial lifetime exposure was developed (U.S. EPA, 1984b). In this model (Thorslund, 1982), a human risk at age t that is due to an exposure of d mg/kg/day from age s to f was estimated from the equation:

$$P(t,d) = 1-e^{-6.958\times10^{-14} \times d \times [(t-s)^{7.6}-(t-f)^{7.6}]} \qquad (6\text{-}1)$$

However, a numerical mistake was found in the derivation of the parameter 6.958×10^{-14} in the Thorslund paper. In deriving the dose correction factor on page 19, the statement was made that 0.59x7/5=0.708, whereas the correct result is actually 0.826. With this correction, the parameter 6.958×10^{-14} becomes 8.228×10^{-14}.

That equation, however, was based upon an equivalency assumption between species on an mg/kg basis. Assuming mg/surface area exposure equivalency, a 70 kg human and a 500 g rat, the exponent in the above equation is multiplied by $(70/0.5)^{1/3} = 5.192$, which gives the result:

$$P(t,d) = 1-e^{-4.215\times10^{-13} \times d \times [(t-s)^{7.6}-(t-f)^{7.6}]} \qquad (6\text{-}2)$$

For continuous lifetime exposure, s=o and t and f are 76.2 years so that the dose-dependence of the lifetime risk becomes:

$$P(d)=1-e^{-85d}$$

where d is the mg/kg/day dose. This is equivalent to a q_1^* value of 85 $(mg/kg/day)^{-1}$ or 0.085 $(\mu g/kg/day)^{-1}$. The water concentration corresponding to a 10^{-4}, 10^{-5} and 10^{-6} lifetime risk is, assuming a drinking water intake of 2 ℓ/day, 4×10^{-2}, 4×10^{-3} and 4×10^{-4} mg/ℓ, respectively. If the exposure duration is less than a lifetime, the risk depends on both the duration and the age of exposure as given in the previous equation.

6.3.2. Inhalation. The NTP (1982) experiment in which a high incidence of tumors in the nasal cavity were observed in rats and a high incidence of

tumors of the respiratory tract were observed in mice is appropriately chosen as the basis for estimation of carcinogenic potency due to inhalation exposure. In keeping with the methodology endorsed by U.S. EPA (1980a) for estimating carcinogenic potencies to humans from animal exposure data, the multistage model was applied to the data presented in Tables 6-1, 6-2, 6-3 and 6-4. The highest human q_1^* is 1.37 $(mg/kg/day)^{-1}$ based on the incidence of tumors of the nasal cavity in male rats (NTP, 1982). This value is chosen to represent the carcinogenic potency of ethylene dibromide to humans exposed by inhalation.

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*

Compound: Ethylene dibromide

Reference: NTP, 1982

Species, Strain, Sex: rat, F344, male

Body weight: 0.300 kg
(estimated from graphic data provided by investigators)[a]

Length of exposure (le) = 88 weeks high dose, 103 weeks low dose

Length of experiment (Le) = 88 weeks high dose, 103 weeks low dose

Lifespan of animal (L) = 104 weeks

Tumor site and type: total tumors of the nasal cavity

Route, vehicle: inhalation

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	0/50
10 ppm (77 mg/m³)[b]	9.0[c,d]	39/50
40 ppm (307 mg/m³)[b]	22.3[c,e]	41/50

Human $q_1^* = 1.37\ (mg/kg/day)^{-1}$[f,g]

[a]Although the investigators reported that body weights of high-dose rats were below those of controls throughout the study, statistical analysis was not performed and visual inspection of graphic data did not suggest that differences were biologically significant.

[b]Exposure 6 hours/day, 5 days/week

[c]*Transformed dose calculated* by expanding to continuous exposure and assuming inhalation volume of $0.105\ (W/0.113)^{2/3}$ (U.S. EPA, 1985c) where W = estimated body weight of 0.300 kg.

[d]Includes a factor of $(103/104)^3$ to convert for less-than-lifetime duration of experiment.

[e]Includes a factor of $(88/104)^3$ to convert for less-than-lifetime duration of experiment.

[f]High dose data dropped to accommodate chi-square goodness of fit.

[g]Includes a factor of $(70/0.300)^{1/3}$ to account for differences in body weight between rats and humans.

TABLE 6-2

Cancer Data Sheet for Derivation of q_1^*

Compound: Ethylene dibromide

Reference: NTP, 1982

Species, Strain, Sex: rat, F344, female

Body weight: 0.225 kg
(estimated from graphic data provided by investigators)[a]

Length of exposure (le) = 91 weeks high dose, 103 weeks low dose

Length of experiment (Le) = 91 weeks high dose, 104 weeks low dose

Lifespan of animal (L) = 104 weeks

Tumor site and type: total tumors of the nasal cavity

Route, vehicle: inhalation

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	1/50
10 ppm (77 mg/m³)[b]	10.1[c]	34/50
40 ppm (307 mg/m³)[b]	27.1[c,d]	43/50

Human $q_1^* = 0.73\ (mg/kg/day)^{-1}$[e]

[a]Although the investigators reported that body weights of high-dose rats were below those of controls throughout the study, statistical analysis was not performed and visual inspection of graphic data did not suggest that differences were biologically significant.

[b]Exposure 6 hours/day, 5 days/week

[c]Transformed dose calculated by expanding to continuous exposure and assuming an inhalation volume of $0.105\ (W/0.113)^{2/3}$ (U.S. EPA, 1985c) where W = estimated body weight of 0.225 kg.

[d]Includes a factor of $(91/104)^3$ to correct for less-than-lifetime duration of experiment.

[e]Includes a factor of $(70/0.225)^{1/3}$ to account for differences in body weight between rats and humans.

TABLE 6-3

Cancer Data Sheet for Derivation of q_1^*

Compound: Ethylene dibromide

Reference: NTP, 1982

Species, Strain, Sex: mouse, B6C3F1, male

Body weight: 0.035 kg control and low group; 0.027 kg high group (estimated from graphic data provided by investigators)

Length of exposure (le) = 78 weeks

Length of experiment (Le) = 78 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: total respiratory tract tumors

Route, vehicle: inhalation

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	0/41
10 ppm (77 mg/m³)[a]	0.6[b,c]	3/48
40 ppm (307 mg/m³)[a]	2.3[c,d]	25/46

Human $q_1^* = 0.21\ (mg/kg/day)^{-1}$

[a]Exposure 6 hours/day, 5 days/week

[b]Transformed dose calculated by expanding to continuous exposure and assuming an inhalation volume of $0.0345(W/0.025)^{2/3}$ where W = estimated body weight of 0.035 kg.

[c]Includes a factor of $(78/104)^a$ and $(0.035/70)^{1/3}$ to correct for less-than-lifetime length of experiment and convert from an animal to human dose in derivation of human q_1^*.

[d]Transformed dose calculated by expanding to continuous exposure and assuming an inhalation volume of $0.0345(W/0.025)^{2/3}$ where W = estimated body weight of 0.027 kg.

TABLE 6-4

Cancer Data Sheet for Derivation of q_1^*

Compound: Ethylene dibromide

Reference: NTP, 1982

Species, Strain, Sex: mouse, B6C3F1, female

Body weight: 0.032 kg control and low group; 0.026 kg high group (estimated from graphic data provided by investigators)

Length of exposure (le) = 103 weeks low dose, 90 weeks high dose

Length of experiment (Le) = 104 weeks low dose, 90 weeks high dose

Lifespan of animal (L) = 104 weeks

Tumor site and type: total tumors of respiratory tract

Route, vehicle: inhalation

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	4/49
10 ppm (77 mg/m³)[a]	1.3[b,c]	11/49
40 ppm (307 mg/m³)[a]	3.5[d,e,f]	42/50

Human $q_1^* = 0.14\ (mg/kg/day)^{-1}$

[a] Exposure 6 hours/day, 5 days/week

[b] Transformed dose calculated by expanding to continuous exposure and assuming an inhalation volume of $0.0345(W/0.025)^{2/3}$ where W = estimated body weight of 0.032 kg.

[c] Human dose estimated from animal data by including a factor of $(0.032/70)^{1/3}$ and $(103/104)^3$ to account for length of the experiment being less-than-lifespan of the mouse.

[d] Transformed dose calculated by expanding to continuous exposure and assuming an inhalation volume of $0.0345(W/0.025)^{2/3}$ where W = estimated body weight of 0.026 kg.

[e] Human dose estimated from animal data by including a factor of $(0.026/70)^{1/3}$

[f] Factor of $(90/104)^3$ included to account for length of experiment less than lifespan.

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APPENDIX

Summary Table for Ethylene Dibromide

Route	Species/ Strain/ Sex	Experimental Exposure/Dose (mg/kg/day)	Effect	q_1^* or Unit Risk $(mg/kg/day)^{-1}$	Reference
Inhalation	rat/F344/ male	0, 10, 40 ppm (0, 77 and 307 mg/m^3), 6 hours/day, 5 days/week for 88-103 weeks (0, 9.0, 22.3 mg/kg/day)[a]	tumors of nasal cavity	1.37	NTP, 1982
Oral	rat/ Osborne-Mendel/ male	49 weeks gavage treatment, 5 days/week resulting in TWA intakes of 0, 27 and 29 mg/kg/day	increased incidence of forestomach tumors	85.0[b]	NCI, 1978; U.S. EPA, 1984b, 1985a

[a]See Table 6-3 for estimation of transformed dose

[b]Estimated from a dose of 8×10^{-4} mg/day, calculated by U.S. EPA (1984b, 1985a), associated with an excess cancer with level of 10^{-5}

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